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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Steven L Highlander
Fulbright & Jaworski
600 Congress Avenue Suite2400
Austin, TX 78701

EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 10/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,549	NIELSEN ET AL.	
	Examiner	Art Unit	
	Lora E Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-40* is/are pending in the application.

4a) Of the above claim(s) *24,26 and 31-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-23, 25, 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/30/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be **clear and concise** and should not repeat information given in the title. **It should avoid using phrases which can be implied**, such as, "The

disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are: "A drug X will disrupt the interaction of effector X with Rab5:GTPgS...used as an inhibitor of effector X in the biological process X" (p.26, lines 11-13 and 33); "which are required in virtually every transport step which has been investigated" (p.1, line 23); and "provides a molecular explanation for the multiplicity of functions of Rab5 and allow to predict similar mechanisms..." (p.2, lines 16-17).

In addition, the entire specification should be checked carefully for grammatical and spelling errors. For example, the name "Christoforidis" is consistently misspelled throughout the specification and references.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-23, 25, and 27-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention. The specification does not enable any person of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

Claims 15-23, 25, and 27-30 depend from claim 14; all are drawn to methods of screening substances for use as pharmaceutical agents for the prophylaxis and/or treatment of, in some dependent claims, at least 45 specific disease types, some of which are caused by specific infectious agents, of which at least 14 are named. Additionally, the claims are drawn to screening substances for use in prophylaxis and/or treatment of broad classes of diseases, i.e. proliferative, invasive, and cell-migration disorders. The examples provided by the applicants, in addition to the claimed screen, are limited to *in vitro* investigations of cell motility, microtubule pelleting, endosome fusion and motility, and construction of cDNA constructs.

While applicants indeed disclose a method for screening substances for effects on GTPase/GTPase effector interactions, no guidance is provided as to the use of said

compounds in the treatment or prophylaxis of any disease, much less in treating the broad and varied classes of diseases and disorders currently claimed. Because of the unpredictable nature of the art, a person of ordinary skill in the art would have a low expectation of success in using the substances resulting from the claimed screen in treating any given condition, including but not limited to those recited in claims 17-21. Applicant has provided no guidance regarding treatment of said disorders, i.e. provisions for diagnosis, dosage regimens, and methods for evaluating efficacy, inter alia, that would reasonably enable one of ordinary skill in the art to have a reasonable expectation of success in using the invention as claimed without substantial further investigation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14, 19, 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 should be amended to recite "...comprising assessing the **effect** of said substance..."

Claim 19 lacks a period.

Claim 22 recites the limitation "the assay" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 14 does not recite an assay.

Claim 23 should be amended to recite "...or **radioactive** label."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(Action continues on page 7)

Claims 14, 17- 22, 25, and 27-30 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. '995 (A). The claims are drawn to a method for screening compounds for effects on interactions between GTPases and their effectors. In some dependent claims, the effector molecule is labeled; in some dependent claims, said molecule is bound to a substrate such as a bead. Some dependent claims are directed toward potential uses for compounds recovered from the screen; other dependent claims describe the types of compounds that can be tested using the screen.

U.S. '995 teaches a method of screening for compounds that inhibit the direct binding of Ras, a GTPase, to its effector protein Raf. In one method of U.S. '995, the Ras effector Raf is recombinantly fused to glutathione-S-transferase (GST) and bound to glutathione sepharose beads. A known amount of Ras GTPase is then contacted with the beads in the absence and presence of a given compound. By measuring the amount of unbound peptide from each sample, the amount of bound peptide can be calculated (column 13, line 56 through column 14, line 21). In this way, compounds that prevent a significant amount of Ras from binding to GST-Raf can be isolated for further study.

Claims 29 and 30 are drawn to a method of screening broad classes of functional groups that may comprise a compound isolated from the assay of claim 14; the specification merely discloses that other compounds useful for therapy of cancer or infectious diseases may possess one or more of said functional groups. No evidence is disclosed as to the patentability of compounds having said groups as opposed to

compounds lacking said groups. Absent evidence to the contrary, testing compounds with one or more of said groups in the assay of claim 14 is anticipated by U.S. '995.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14, 17-22, 25 and 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. '995. The claims are drawn to a method for screening compounds for effects on interactions between GTPases and their effectors, as described above under 35 U.S.C. § 102(b).

U.S. '995 teaches a method of screening for compounds that inhibit the direct binding of Ras, a GTPase, to its effector protein Raf, as described above under 35 U.S.C. § 102(b). U.S. '995 does not specifically recite screening β-hydroxy carboxylic acids with said method.

Accordingly, one of ordinary skill in the art would have had a reasonable expectation of success in screening β-hydroxy carboxylic acids with the assay of U.S. '995 because said assay can be used to screen any "candidate compound" (column 13, line 56 – column 14, line 22). Absent evidence to the contrary, there is no distinguishing feature of β-hydroxy carboxylic acids that precludes their being screened using said assay.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to screen β-hydroxy carboxylic acids with the assay of U.S. '995 because it is common practice in the art to screen millions of compounds with diverse chemical structure using a single assay. The skilled artisan would have been motivated to make said modification because pharmaceutical compounds may comprise β-hydroxy carboxylic acid groups. Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made.

Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. '995 as applied to claims 14, 17- 22, 25, and 27-30, above, and in view of Touchot et al. (U). The claims are drawn to a method for screening compounds for effects on interactions between GTPases and their effectors, specifically Rab GTPases, and more specifically the endosomally localized Rab4, Rab5, Rab7, Rab11, Rab17, Rab18, and Rab22. U.S. '995 teaches a method for screening compounds for effects on interactions between the GTPase Ras and its effector Raf, but do not specifically teach said method for Rab proteins.

Touchot et al. teach the Rab family of proteins, the encoding DNA sequences of which were identified from a rat brain cDNA library as being able to hybridize to a conserved motif from *S. cerevisiae* YPT1, the yeast homolog of Ras. Touchot et al. further analyze the amino acid sequences of several Rab proteins and teach that "the *rab* genes [clearly] belong to a third branch of the *ras* superfamily distinct from the *ras* protooncogenes and from the *rho* family" (p.8212, second paragraph). The teachings of Touchot et al. as well as other skilled artisans indicate that Ras, Rho, and Rab proteins have similar types of functions in signal transduction, cytoskeletal remodeling, and cell motility; Rab proteins, like all Ras superfamily proteins, hydrolyze GTP and are regulated by the activity of various effectors.

Accordingly, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the Rab proteins of Touchot et al. and their effectors into the assay of U.S. '995 because it is well known in the art that Ras superfamily proteins' interactions with effector molecules are essential to appropriate

regulation of these GTPases. Numerous Rab proteins and their effectors have been cloned and placed into expression vectors, and the person of ordinary skill in the art could readily adapt the method of U.S. '995 to any GTPase-GTPase effector pair.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use Rab proteins and their effectors in the assay of U.S. '995 for the expected benefit of discovering compounds that specifically target particular functions of a given Rab protein, potentially providing therapy for diseases resulting from faulty endosome trafficking. Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made.

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. '995 as applied to claims 14, 17- 22, 25, and 27-30, above, and in view of Yao et al. (1994, Journal of Virology 68:8158-8168) and Park et al. (1997, Protein Science 6:2344-2349). The claim is drawn to a method of assessing the effect of various compounds on interactions between a GTPase and its effector, more specifically a radioactive or fluorescently labeled effector. U.S. '995 does not specifically teach a method for assessing protein-protein interactions using radioactive or fluorescently labeled proteins.

Yao et al. teach an *in vitro* method for detecting the interaction between two HSV type I proteins, ICP0 and ICP4, comprising GST-ICP0 immobilized on a column and further adding *in vitro* translated ICP4 comprising radioactive ^{35}S-methionine. Park et al.

teach that green fluorescent protein, GFP, is a useful label in methods for detecting protein-protein interactions.

Accordingly, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the radioactive label of Yao et al. or the GFP label of Park et al. into the compound screen of U.S. '995 because said labels are well known in the art to increase precision and range of detection in interaction assays. The method of U.S. '995 seemingly involves quantitating free protein, a technique with a high level of inherent error and low range of detection; using fluorescent or radioactive labels are an obvious modification of the method of U.S. '995.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use a fluorescent or radioactive label in an assay of GTPase-GTPase effector interactions for the expected benefit of more precisely and accurately determining whether a given compound affects said interaction. Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made.

No claims are allowed. No claims are free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lora E Barnhart

SANDRA E. SAUCIER
PRIMARY EXAMINER